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## Chirality and catalysis with aromatic N-fused heterobicyclic carbenes

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The benzoannulation of the most common families of aromatic NHCs, imidazol-2-ylidenes and 1,2,4-triazol-3-ylidenes, results in heterobicyclic imidazo[1,5-*a*]pyridin-3-ylidenes (**ImPy**'s) and [1,2,4]triazolo-[4,3-*a*]pyridin-3-ylidenes (**TriPy**'s), characterized by a bridged N atom. These are versatile platforms that offer multiple possibilities for the modulation of the steric and electronic properties of the carbene ligand and/or organocatalyst, and offer also diverse opportunities for the introduction of several types of chiralities. In this paper the different families of chiral **ImPy** and **TriPy** carbenes and their application in asymmetric catalysis will be discussed.

## Introduction

N-heterocyclic carbenes (NHCs) constitute a well-established type of ligand in transition-metal catalysis.<sup>1</sup> Characterized by strong  $\sigma$ -donor and variable  $\pi$ -acceptor properties,<sup>2</sup> these ligands typically provide high thermal and chemical stability to their complexes. Additionally, the steric properties of NHCs are intrinsically distinct from those of phosphines,<sup>3</sup> the alternative family of strongly  $\sigma$ -donating ligands. Together, these are an appealing set of properties for applications in the field of asymmetric catalysis, and, consequently, many laboratories have developed strategies for the introduction of chiral elements, making NHCs the ligand of choice for a number of metal-catalysed asymmetric transformations.<sup>4</sup> Additionally, NHCs have also recently emerged as a useful class of Lewis bases that have found a plethora of applications in asymmetric organocatalysis.<sup>5</sup> Since the isolation of Arduengo's first stable imidazol-2-ylidene,<sup>6</sup> numerous classes of structurally and electronically diverse NHC structures have been reported.<sup>7</sup> One of the strategies used to modify the steric and electronic properties of these ligands has been the inclusion of the diaminocarbene system into a heterobicyclic skeleton. In 2005, we<sup>8</sup> and Glorius<sup>9</sup> independently reported the synthesis and coordination properties of heterobicyclic imidazo[1,5-*a*]pyridin-3-ylidenes (**ImPys**). Some years later, the synthesis

and coordination behavior<sup>10</sup> of [1,2,4]triazolo[4,3-*a*]pyridin-3-ylidenes (**TriPys**), along with an evaluation of their properties as organocatalysts<sup>11</sup> were also reported (Fig. 1). Since then, a number of imidazo/triazolo pyridinium salts and their corresponding NHCs have been developed. In this paper we will focus on the different strategies reported to introduce chirality into carbene ligands, complexes, and catalysts based on the structures of these aromatic N-fused heterobicyclic scaffolds, along with their applications in asymmetric catalysis.

## Discussion

Three different strategies have been developed for the synthesis of imidazo[1,5-*a*]pyridinium salts (**ImPy**-HX), direct precursors of the free **ImPy** carbenes and/or ligands: *N*-alkylation of imidazo[1,5-*a*]pyridines,<sup>8</sup> cyclisation of 2-formamidomethyl pyridines by phosphoryl chloride<sup>8</sup> or  $\text{Ti}_2\text{O}/\text{Et}_3\text{N}$ ,<sup>12</sup> and cyclisation of picolinaldimines using a 1 : 1 mixture of  $\text{AgOTf}$  and chloromethyl pivalate, although this last method provided the products in moderate yields.<sup>9</sup> Already in the original report,  $C_2$ -symmetric 'chiral at the metal' cationic  $\text{Rh}^{\text{I}}$  bis-carbenes  $[\text{Rh}(\text{COD})(\text{ImPy})_2]^+\text{X}^-$  were selectively formed in the reaction of *N*-alkyl/aryl imidazo[1,5-*a*]pyridinium hexafluorophosphates with  $\text{KO}^t\text{Bu}$  and  $[\text{Rh}(\text{COD})\text{Cl}]_2$ , while no trace of the *meso* isomers was detected (Scheme 1). These complexes, however, were obtained in the racemic form and have not yet been resolved.

First examples of homochiral imidazo[1,5-*a*]pyridin-3-ylidenes were later incorporated as  $\text{C}(\text{ImPy})/\text{S}$  ligands into complexes  $[\text{M}(\text{ImPy})_2]$ .<sup>13</sup> The azolium salts

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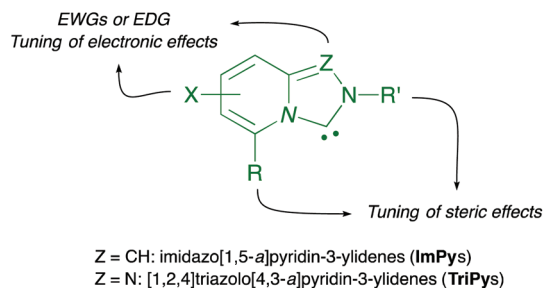
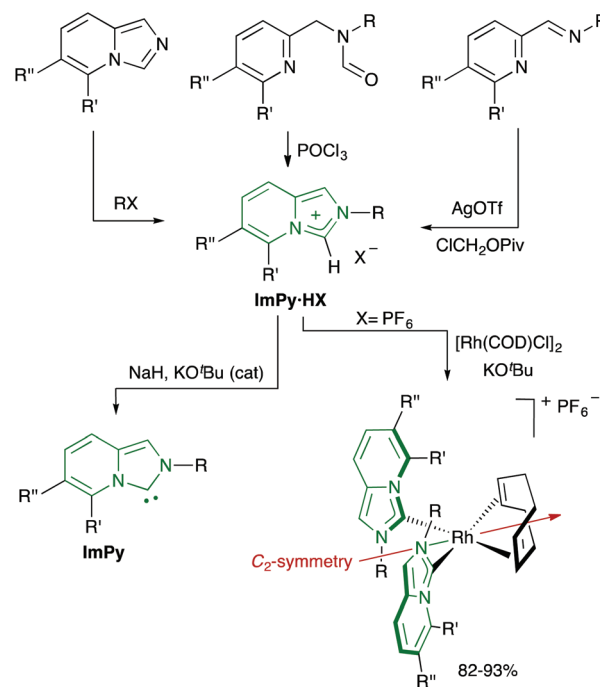


Fig. 1 Structures and tuning elements of N-fused heterobicyclic carbenes.

**ImPy2**·HX<sup>†</sup> were metalated with Ag<sub>2</sub>O according to the popular method by Lin,<sup>14</sup> and the resulting [(**ImPy2**)AgX] complexes (Scheme 2) were used as carbene transfer agents in near quantitative transmetalations to [Pd(η<sup>3</sup>-allyl)(COD)]<sup>+</sup>SbF<sub>6</sub><sup>−</sup> to afford the target cationic complexes [(**ImPy2**)Pd(η<sup>3</sup>-allyl)]<sup>+</sup>SbF<sub>6</sub><sup>−</sup>, in which the absolute configuration at the coordinated sulphur atom is controlled by the relative *trans* geometry between the cyclohexyl and isopropyl groups, forced to avoid severe steric

<sup>†</sup>The methods used for the synthesis of imidazo/triazolo pyridinium salts are those mentioned previously and illustrated in Scheme 1, or slight modifications of them, and will be omitted for any other examples shown.



Scheme 1 Synthesis of imidazo[1,5-a]pyridin-3-ylidenes and C<sub>2</sub>-symmetric Rh<sup>I</sup> complexes.



From left to right appear: Cristina Izquierdo, Elena Díez, Javier Iglesias-Sigüenza, Rosario Fernández and José M. Lassaletta

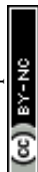
Javier Iglesias-Sigüenza received his PhD in 2009 at the University of Sevilla. Then he joined the group of Prof. M. Alcarazo at the Max-Planck-Institut für Kohlenforschung of Mülheim an der Ruhr (Germany, 2011–2012). In 2012 he returned to the University of Sevilla, where he was appointed as Assistant Professor. His current research interests include synthesis of chiral N-heterocyclic carbenes and their application in asymmetric catalysis.

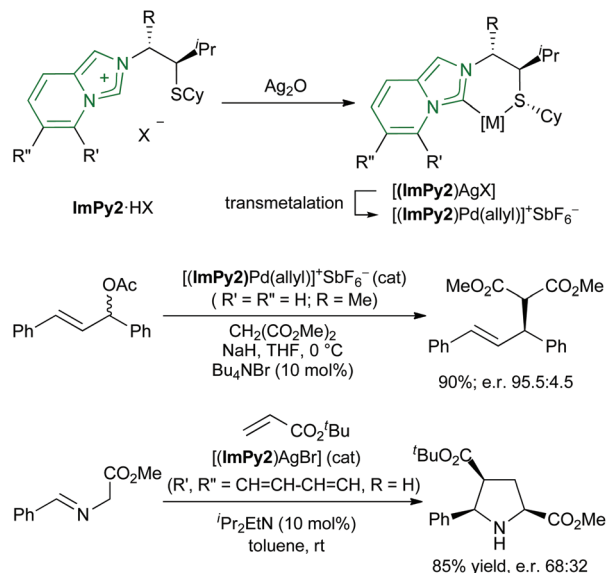
Cristina Izquierdo studied Chemistry at the Universidad Autónoma de Madrid (UAM) and received her BS degree in 2011. A year later she finished her M.S. and she is now pursuing her Ph.D. degree in the R. Fernández and J. M. Lassaletta group at the University of Sevilla. Her research interest focuses on the use of N-heterocyclic carbenes in asymmetric catalysis.

Elena Díez received her PhD in 1998 at the University of Sevilla. Then she spent three years as a postdoctoral fellow at the University of Cambridge in the group of Prof. Steven V. Ley. In 2002 she returned as a 'Ramón y Cajal' fellow at the University of Sevilla, where she was promoted to Associate Professor in 2009. Her current research interests include asymmetric metal catalysis and organocatalysis based on N-heterocyclic carbenes.

Rosario Fernández studied chemistry at the University of Sevilla and received her PhD degree (1985) under the supervision of Prof. Antonio Gómez Sánchez. She was a NATO postdoctoral fellow at the University of Paris-Sud (Orsay, France) in the laboratory of Prof. Serge David from 1986 to 1987. Then she returned to the University of Sevilla as Associate Professor and promoted to full Professor in 2008. Her current research interests include asymmetric synthesis, asymmetric metal catalysis and organocatalysis.

José María Lassaletta received his PhD in 1990 from the University of Sevilla. After a postdoctoral stage in the 'Instituto de la Grasa y sus Derivados' (CSIC, Sevilla) he joined the group of Professor Richard R. Schmidt (U. Konstanz, Germany). In 1995 he moved to the Instituto de Investigaciones Químicas (CSIC, Sevilla), where he was promoted to Tenured Scientist in 1996, Research Scientist in 2005 and Research Professor in 2009. He is currently interested in the development of synthetic methodologies, cross-coupling and C–H activation strategies, and ligand design (with emphasis on hydrazones and N-heterocyclic carbenes), and asymmetric organocatalysis.



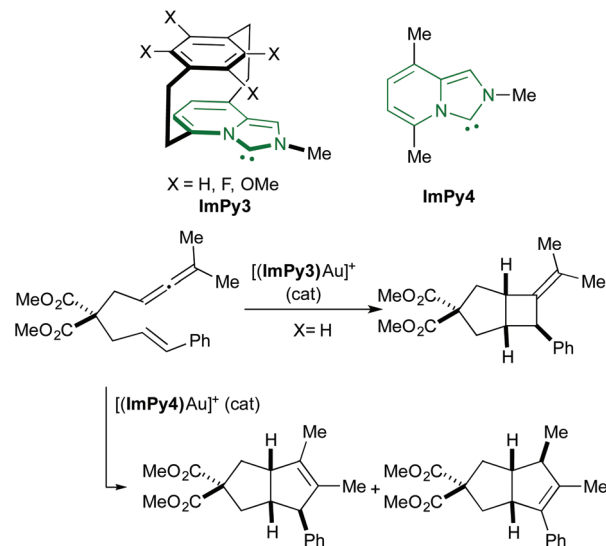


Scheme 2 Applications of heterobidentate C(ImPy2)/S ligands.

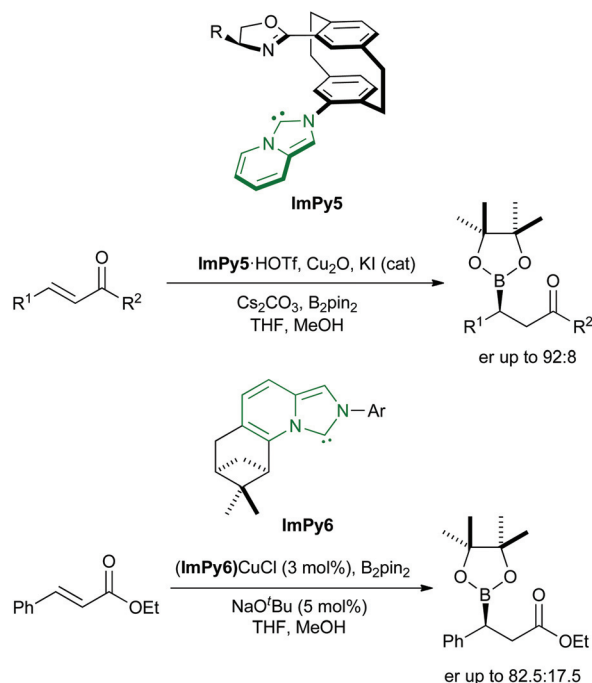
interactions. These complexes were successfully used as precatalysts in Pd<sup>0</sup>-catalysed asymmetric allylic alkylations, reaching enantioselectivities up to 95.5:4.5 er. The parent silver complexes  $\text{[(ImPy2)AgX]}$  were also used as catalysts in the 1,3-dipolar cycloaddition of iminoglycinates, although, in this case, best results were obtained with C<sub>2</sub>-symmetric S/C/S imidazo[1,5-a]pyridine ligands.<sup>15</sup> This was the first example of the use of silver carbenes in asymmetric catalysis.

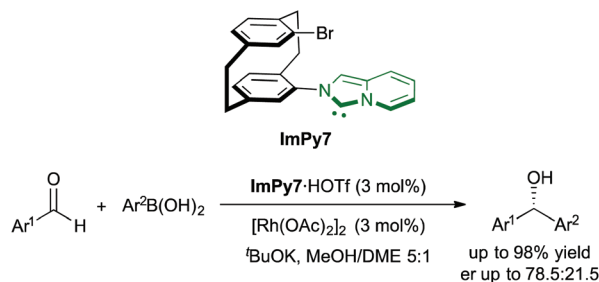
An elegant example of effective electronic modulation of NHC ligands was described by Fürstner and co-workers by embedding the imidazo[1,5-a]pyridin-3-ylidene system **ImPy3** into a planar chiral [2,2]-paracyclophane scaffold.<sup>16</sup> Measurements and calculations of the electronic properties of these ligands revealed that remote electronic variations [achieved by substitution on the cyclophane benzene unit (X = H, F, OMe)] can be transmitted within the cyclophane scaffold to the carbene bonding orbitals. With respect to a simple **ImPy4** analogue, this type of ligand possesses similar (but tuneable) σ-donor abilities, but much stronger π-acidity. Interestingly, this characteristic has been used to control the fate of the intramolecular gold(i)-catalysed cycloisomerization of enallenes (Scheme 3), among the other ligand-driven catalytic reactions.<sup>17</sup> In spite of their high synthetic potential, however, the resolution and application of these planar-chiral ligands in asymmetric catalysis remain unexplored.

A second example of a planar chiral imidazo[1,5-a]pyridinylidene family **ImPy5** based on [2,2]paracyclophanes was reported in 2011 by Ma and co-workers.<sup>18</sup> Unlike the precedent case, the **ImPy** unit is simply attached to a cyclophane structure, not constituting an integral part of the stereogenic unit. These carbenes combine the planar chirality of [2,2]paracyclophane with the central chirality of oxazolines to build heterobidentate C/N ligands. The authors examined their application in enantioselective conjugate β-boration of chalcones

Scheme 3 Chiral planar **ImPy3** ligands with tuneable π-acceptor character.

(Scheme 4). Best results were obtained with catalysts  $\text{[(ImPy5)Cu]}$  prepared *in situ* from the azolium triflate **ImPy5-HOTf**, Cu<sub>2</sub>O and KI. In a related example,<sup>19</sup> the chiral  $\text{[(ImPy6)CuCl]}$  complex derived from β pinene was used for the asymmetric β-boration of ethyl cinnamate, although with lower enantioselectivities (er up to 82.5:17.5). Similar planar chiral [2,2]paracyclophanyl imidazo[1,5-a]pyridinium salts have been described as precursors of NHCs **ImPy7** (Scheme 5)<sup>20</sup> and their

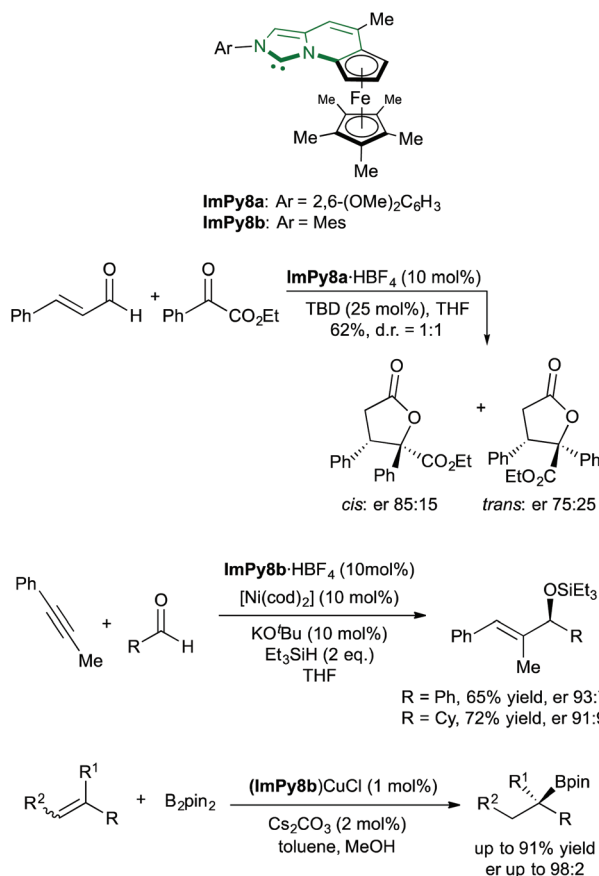
Scheme 4 (ImPy)Cu<sup>I</sup>-catalysed asymmetric β-boration of electron-poor alkenes.



**Scheme 5** (ImPy7)Rh<sup>I</sup>-catalysed asymmetric addition of arylboronic acids to aldehydes.

rhodium complexes have been tested in the asymmetric 1,2-addition of arylboronic acids to aldehydes, although, providing moderate enantioselectivities (er up to 78.5 : 21.5).

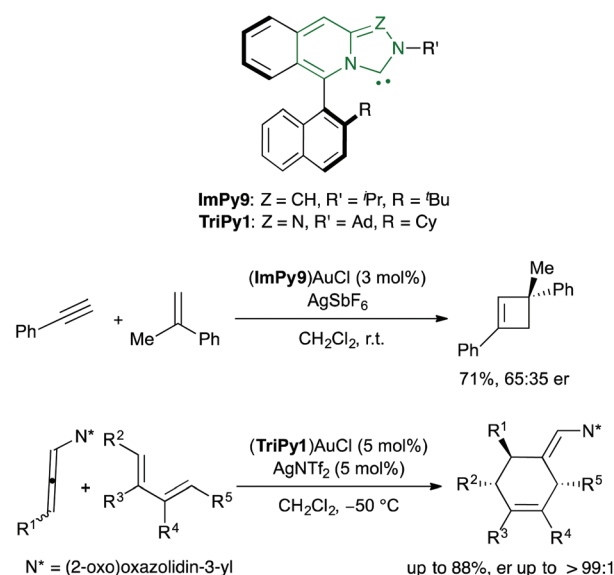
Very recently, Scheidt and co-workers have reported on the synthesis and applications of ferrocene-based planar chiral imidazopyridinium salts **ImPy8**-HX (Scheme 6).<sup>21</sup> In this novel NHC design, the **ImPy** unit is fused with an iron sandwich complex to provide a strong facial bias. Several challenging applications were explored for these new types of **ImPys**. The free carbenes, generated *in situ* from tetrafluoroborates **ImPy8**-HBF<sub>4</sub> by deprotonation with 1,5,7-triazabicyclo [4.4.0]



**Scheme 6** Applications of ferrocene-based planar chiral **ImPy8** carbenes.

dec-5-ene (TBD) as the base were used in homoenolate additions to  $\alpha$ -ketoesters. Best results were obtained with the 2,6-dimethoxyphenyl derivative **ImPy8a**-HBF<sub>4</sub>, which provided the highest level of enantioselectivity (er 85 : 15 for the *cis* diastereomer), although without any diastereoselectivity (dr = 1 : 1). Their evaluation as ligands for transition-metal complexes was also reported. As a first example, the **ImPy8b** ligand (Ar = Mes) was used in the nickel-catalysed reductive coupling of 1-phenyl-1-propyne with aldehydes using triethylsilane as the reducing agent. The enantioselectivities observed [er 93 : 7 and 91 : 9] for benzaldehyde and cyclohexanecarboxaldehyde, respectively matched or improved those previously reported for this challenging transformation. Finally, the preformed [(**ImPy8b**)CuCl] complex was also used as a catalyst in the borylation of olefins, which proceeded with high enantioselectivities for a variety of substrates.

The fixed orientation of the diaminocarbene lone pair (or the C(carbene)–metal bond) in **ImPy** or **TriPy** ligands and complexes makes also attractive the integration of these systems into an axially chiral biaryl scaffold, with the stereogenic axis located at C(5). In particular, ligands such as **ImPy9** and **TriPy1** are well suited to project the asymmetric environment to the antipodes of the carbene carbon in linear Au<sup>I</sup> complexes (Scheme 7). Preliminary results on the unprecedented asymmetric [2 + 2] cycloaddition between styrenes and alkynes were achieved by using [(**ImPy9**)Au]<sup>+</sup>SbF<sub>6</sub><sup>−</sup> complexes, leading to the expected cyclobutenes in good yields but modest enantioselectivities.<sup>22</sup> On the other hand, the combination of an enhanced  $\pi$ -acidity in **TriPy1** ligands (provided by the additional N atom in the heterocycle) and a high level of facial discrimination attributed to steric factors allowed us to perform [(**TriPy1**)Au]<sup>+</sup>-catalysed intermolecular [4 + 2] cycloadditions of allenamides and dienes, leading to the desired



**Scheme 7** Applications for axially chiral (ImPy/TriPy)AuX complexes in asymmetric catalysis.





carbocycles with up to three newly created stereogenic centers in excellent yields and enantioselectivities (er's up to >99 : 1).<sup>23</sup>

## Conclusions

In conclusion, N-fused heterobicyclic imidazo- and triazolo pyridin-3-ylidene architectures have emerged as versatile platforms that enable multiple strategies for the introduction of chirality<sup>24</sup> and the tuning of steric and electronic effects, in both cases facilitated by their modular structures. While some challenging applications have been already successfully discovered, the potential of these ligands and complexes in asymmetric catalysis is clearly underdeveloped. Some of the structures shown are particularly promising in fields such as Au(NHC)-catalysed reactions or organocatalysis, among others.

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